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(54) Title: ANTI-HYPERCHOLESTEROLEMIC DRUG COMBINATION

(57) Abstract: This invention provides a drug combination comprised of an HMG-CoA reductase inhibitor with an ACAT inhibitor in synergistic therapeutically effective amounts, which is useful for reducing cholesterol synthesis, lowering plasma LDL cholesterol levels and lowering plasma triglyceride levels. Profound synergy can be achieved only when the ACAT inhibitor is administered in low dosage amounts, above which the beneficial synergistic effects diminish and disappear.

TITLE OF THE INVENTION
ANTI-HYPERCHOLESTEROLEMIC DRUG COMBINATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to US provisional application SN 60/157,184, filed September 30, 1999, herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

The instant invention involves a drug combination comprising a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor in combination with a compound which inhibits acyl-coenzyme A:cholesterol acyltransferase (ACAT).

BACKGROUND OF THE INVENTION

Acyl-coenzyme A: cholesterol acyltransferase (ACAT) catalyzes the transfer of a fatty acid to the hydroxyl group of cholesterol that therefore becomes an ester. Since cholesterol esters are a key component of the atherosclerotic plaque and since cholesterol esterification may contribute to regulate cholesterol absorption, ACAT inhibitors have been sought as a drug development candidate by a large number of pharmaceutical houses over the past 20 years. However, when ACAT inhibitor agents with desirable potency such as Dup128 (see Hainer, J., et al., *Effects of the acyl-CoA:cholesterol acyltransferase inhibitor DuP 128 on cholesterol absorption and serum cholesterol in humans*, Clinical Pharmacology & Therapeutics *56*:65-74, 1994) and CI-1011 (Koren, M., et al:, *ACAT inhibitor Avasimibe lowers VLDL-C and triglyceride in patients with hypertriglyceridemia*, Circulation, *98*, Supplement I, I-240, 1998) were brought to the clinic, they failed to show efficacy in cholesterol lowering. This lack of cholesterol lowering efficacy in humans could be explained based on that ACAT inhibitors were shown to be effective lipid lowering agents in preclinical models where animals were fed a diet containing high levels of cholesterol. ACAT inhibitors block absorption of cholesterol when the uptake mechanism is overloaded, but were relatively ineffective in the presence of normal levels of dietary cholesterol. Because of the absence of significant lowering of plasma cholesterol, the dominant contribution of ACAT inhibitors for the prevention and/or treatment of atherosclerosis is currently thought to be through the inhibition of cholesterol ester synthesis in the artery wall.

Recent work has demonstrated the existence of two distinct ACAT genes commonly referred to as ACAT-1 (sometimes referred to as ACAT I), described in U.S. Patent No. 5,834,283, issued November 10, 1998, and ACAT-2 (sometimes referred to as ACAT II), described in WO 97/45439 published December 4, 1997. ACAT-1 is broadly distributed (though exceptionally high in adrenal), while ACAT-2 is restricted to liver and small intestine. Moreover, the deduced structures suggest that the broadly distributed ACAT-1 may have its catalytic domain facing the cytoplasm for the manufacture of cytoplasmic cholesterol ester droplets while the ACAT-2 gene found in lipid-exporting cells apparently may have its catalytic domain facing the lumen of the endoplasmic reticulum for the manufacture of lipoprotein cholesterol esters. Specific inhibitors of ACAT-2 might be expected to block intestinal absorption and hepatic export of cholesterol. On the other hand, ACAT-2 specific inhibitors would not be expected to have effects on cholesterol ester synthesis in foam cells of atherosclerotic lesions. While theoretically possible, neither ACAT-1 nor ACAT-2 specific inhibitors have been shown to lower plasma cholesterol in humans. Importantly, both ACAT-1 and ACAT-2 are found in the endoplasmic reticulum (ER) of cells and act on free cholesterol in the endoplasmic reticulum thereby lowering the free cholesterol concentration in this organelle.

HMG-CoA reductase is the rate-limiting enzyme for the synthesis of cholesterol. Inhibitors of HMG-CoA reductase such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin lower plasma cholesterol and particularly low density lipoprotein (LDL) cholesterol, a major risk factor for atherosclerosis and coronary heart disease. The mechanism of LDL cholesterol lowering by HMG-CoA reductase inhibitors has been shown to involve an hepatic response to cholesterol deprivation. Hepatic cholesterol levels are sensed in the ER by the regulatory proteins, SCAP and SREBP (see Brown, M.S. and Goldstein, J.L., *The SREBP pathway: Regulation of Cholesterol metabolism by proteolysis of a membrane-bound transcription factor*, 1997, Cell *89*: 331-340). When the levels of ER cholesterol are low, SREBP is cleaved, liberating a transcription factor that raises the level of LDL-receptor as well as the levels of enzymes involved in cholesterol synthesis. The increased levels of hepatic LDL receptors, and therefore the relative increased capacity to upload cholesterol from the plasma into the liver, are thought be the principal contributor to plasma LDL cholesterol lowering.

Inhibition of both HMG-CoA reductase and ACAT may have profound direct and indirect effects conducive to prevent or reduce atherogenesis. HMG-CoA

reductase inhibitors lower plasma cholesterol by reducing its concentration in LDL and other lipoproteins such as very low density (VLDL) and intermediate density (IDL) lipoproteins, while ACAT inhibitors prevent cholesterol ester formation primarily in the artery wall. However, current understanding of cholesterol metabolism suggests that ACAT inhibitors and HMG-CoA reductase inhibitors should have less than additive effects on plasma LDL cholesterol levels. The reason for this relates to the subcellular location and function of the proteins involved in reducing LDL cholesterol levels. Inhibition of ACAT in the ER is expected to raise the level of free cholesterol in the ER. The free cholesterol in the ER is then sensed by SCAP and SREBP. That process is predicted to prevent SREBP cleavage and to prevent the rise in LDL receptor, thus blunting the effect of an HMG-CoA reductase inhibitor, thereby suggesting against the combined use of an HMG-CoA reductase inhibitor with an ACAT inhibitor.

Surprisingly, profound synergy has been discovered between ACAT inhibitors and HMG-CoA reductase inhibitors in plasma cholesterol lowering and in lowering of plasma triglycerides. Indeed, under conditions in which HMG-CoA reductase inhibition alone causes modest increases in plasma triglycerides, addition of ACAT inhibitors reverses this effect and results in a profound lowering of plasma triglycerides. Finally, it has been discovered that the profound synergy in cholesterol lowering is only observed with low doses of ACAT inhibitors. When high doses of ACAT inhibitors are used in combination with HMG-CoA reductase inhibitors, cholesterol lowering is abolished or even reversed, as would be expected from the known function of ACAT and SREBP in the ER. Since LDL cholesterol comprises the bulk of total plasma cholesterol in humans, it is believed that the combination of a low dose ACAT inhibitor with an HMG-CoA reductase inhibitor will have a synergistic LDL cholesterol lowering effect in humans.

SUMMARY OF THE INVENTION

The instant invention provides a drug combination comprised of an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in therapeutically effective amounts, which is useful for lowering plasma triglyceride levels.

The instant invention further provides the drug combination comprised of an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts, which is useful for reducing cholesterol synthesis, lowering plasma cholesterol levels, particularly plasma LDL cholesterol levels, and

lowering plasma triglyceride levels. Importantly, it has been discovered against expectations that profound synergy can be achieved only when the ACAT inhibitor is administered in low dosage amounts, above which the beneficial synergistic effects diminish and disappear. Therefore, one object of the instant invention is to administer the above-described synergistic combination therapy to patients who want to reduce their LDL cholesterol level and/or reduce their triglyceride level.

The drug combination is also useful for treating, preventing, and/or reducing the risk of developing atherosclerosis and atherosclerotic disease events. Another object of the instant invention is to administer the above-described combination therapy to people who do not yet show clinical signs of atherosclerosis, but who are at risk of developing atherosclerosis and associated diseases. Clinical manifestations of atherosclerosis include atherosclerotic cardiovascular disease such as coronary heart disease (also known as ischemic heart disease), cerebrovascular disease, and peripheral vessel disease. Toward this end, the instant invention provides methods for preventing or reducing the risk of developing atherosclerotic cardiovascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease, and preventing or reducing the risk of a first or subsequent occurrence of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication, by administering the above-described combination therapy to said at-risk persons.

Another object of the instant invention is to provide the above-described combination therapy to people who have clinical signs of atherosclerosis. Toward this end, the instant invention provides methods for halting or slowing the progression of atherosclerotic cardiovascular disease, coronary heart disease, ischemic heart disease, cerebrovascular disease and peripheral vessel disease, and preventing or reducing the risk of a first or subsequent occurrence of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication, by administering the above-described combination therapy to said persons who have clinically manifest atherosclerotic disease.

A further object of the instant invention involves the above-described methods further comprising the administration of one or more additional active agents either in separate or combined dosage formulations. A still further object is to provide pharmaceutical compositions that can be used in the above-described methods. Additional objects will be evident from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a bar graph showing the cholesterol lowering results of simvastatin, compound (i), compound (vi) and combinations of simvastatin with compounds (i) and (vi) in hamsters.

DETAILED DESCRIPTION OF THE INVENTION

The instant invention provides methods for reducing cholesterol synthesis, lowering plasma cholesterol, particularly lowering plasma LDL cholesterol, lowering plasma triglycerides, and for preventing onset or reducing the risk of developing atherosclerosis, as well as for treating, i.e., halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient who is in need of such treatment, and particularly to a patient at risk of developing atherosclerosis or who already has atherosclerotic disease.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

The combination comprised of an HMG-CoA reductase inhibitor and a low dosage amount of an ACAT inhibitor may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease event are at risk for recurrence of such an event.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic prophylactically effective amounts to a patient at risk for such an event. The patient may already have atherosclerotic disease at the time of administration, or may be at risk for developing it.

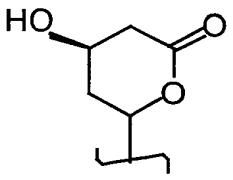
The instant invention also provides a method for preventing and/or treating inflammatory diseases or disorders alone or in conjunction with the treatment of conditions described above, comprising the administration of the instant drug combination therapy to a patient in need of such treatment. This includes, for example, the treatment of inflammatory conditions susceptible to treatment with a non-steroidal anti-inflammatory agent, arthritis including rheumatoid arthritis, and degenerative joint diseases (osteoarthritis), Alzheimer's disease, multiple sclerosis, inflammatory bowel disease, asthma, psoriasis, systemic lupus erythematosis, vasculitis, gout, adrenoleukodystrophy, and diabetic retinopathy.

Persons to be treated with the instant combination therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited to hypertension, smoking, diabetes, high levels of LDL-cholesterol, low levels of high density lipoprotein (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol Education Program, Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; abbreviated version: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA, 1993, 269, pp. 3015-23. People who are identified as having one or more of the above-noted risk factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within

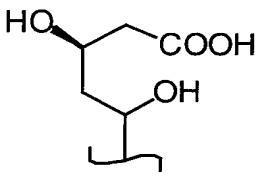
the group of people considered to be at risk for having an atherosclerotic disease event.

A compound that inhibits HMG-CoA reductase is used in combination with an ACAT inhibitor to practice the instant invention. Compounds that have inhibitory activity for HMG-CoA reductase can be readily identified using assays well known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33, herein incorporated by reference.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see US Patent No. 4,231,938), simvastatin (ZOCOR®; see US Patent No. 4,444,784), pravastatin (PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin (LESCOL®; see US Patent No. 5,354,772), atorvastatin (LIPITOR®; see US Patent No. 5,273,995), cerivastatin (also known as rivastatin; see US Patent No. 5,177,080), nisvastatin (also known as itavastatin or NK-104, see U.S. Patent No.s 5,284,953, 5,356,896 and 5,856,336), and ZD-4522 (see US Patent No. 5,260,440). The hemi-calcium salt of NK-104 is described and claimed in U.S. Patent No. 5,856,336, and ZD-4522 is described in Drugs of the Future, 1999, 24(5), pp. 511-513, while the structural formulas of the other noted HMG-CoA reductase inhibitors, as well as additional examples of HMG-CoA reductase inhibitors, are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996). In general, HMG-CoA reductase inhibitors belong to a structural class of compounds which contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding 3,5-dihydroxy open-acid, and are commonly referred to as "statins." The lactone portion of the statin and its corresponding dihydroxy open-acid form is shown below.



Lactone



Dihydroxy Open-Acid

The term HMG-CoA reductase inhibitor is intended to include all lactone and open-ring 3,5-dihydroxy open-acid forms of HMG-CoA reductase inhibitors and the pharmaceutically acceptable salts and esters thereof; and therefor the use of such

lactone and open-ring 3,5-dihydroxy acid forms and salts and esters thereof are included within the scope of this invention. Preferably, the HMG-CoA CoA reductase inhibitor is selected from lovastatin and simvastatin, which are lactonized statins, and their corresponding dihydroxy open acid forms and the pharmaceutically acceptable salts and esters thereof, and most preferably it is selected from simvastatin and its dihydroxy open acid form and the pharmaceutically acceptable salts and esters thereof, including for example the calcium and ammonium salts thereof.

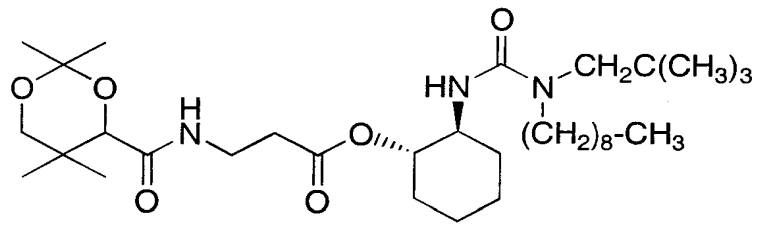
Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, morpholine, 2,4,4-trimethyl-2-pentamine and tris(hydroxymethyl)-aminomethane. Pharmaceutically acceptable esters at the carboxylic acid group can be made by treating a dihydroxy open acid statin with an alcohol. Examples of pharmaceutically acceptable esters of dihydroxy open acid statins include, but are not limited to, -C_{1-4} alkyl and - C_{1-4} alkyl substituted with phenyl-, dimethylamino-, and acetylamino. "C_{1-4} alkyl" herein includes straight or branched aliphatic chains containing from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, n-butyl, *iso*-propyl, *sec*-butyl and *tert*-butyl. Ester derivatives of the described compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

A compound that inhibits ACAT is used in combination with an HMG-CoA reductase inhibitor to practice the instant invention. Compounds which have inhibitory activity for ACAT can be readily identified by using assays well-known in the art, for example as described in Chang C.C., Lee C.Y., Chang, E.T., Cruz, J.C., Levesque, M.C., Chang, T.Y.: J. Biol. Chem. ;273: 35132-35141, 1998: *Recombinant acyl-CoA:cholesterol acyltransferase-1 (ACAT-1) purified to essential homogeneity utilizes cholesterol in mixed micelles or in vesicles in a highly cooperative manner*, herein incorporated by reference. Compounds which inhibit each of the isoforms of ACAT are included within the scope of this invention; for example compounds which

selectively inhibit ACAT-1 or ACAT-2, and particularly compounds which have dual inhibitory activity for both ACAT-1 and ACAT-2, are useful with the present combination. Pharmaceutically acceptable salts and esters of ACAT inhibitors are likewise included within the scope of this invention.

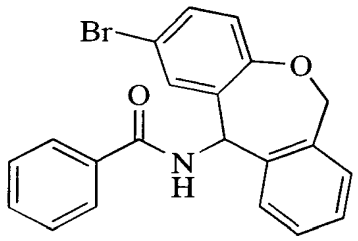
Compounds which are ACAT inhibitors include but are not limited to those described in (i) U.S. Patent No. 5,120,738 assigned to Fujirebio, Inc.; (ii) U.S. Patent No. 5,340,807 assigned to Kyowa Hakkpo, Kogyo Co., Ltd.; (iii) U.S. Patent No. 5,475,130 assigned to Taisho Pharmaceutical Co., Ltd.; (iv) U.S. Patent No. 5,668,136 assigned to Eisai Co., Ltd.; (v) U.S. Patent No. 5,760, 087 assigned to Pierre Fabre Medicamemt; (vi) WO96/26925 applied for by Banyu Pharmaceutical Co., Ltd.; (vii) Sliskovic, D.R., *CI-1011: An atypical ACAT inhibitor with antiatherosclerotic activity*, Proceedings, XIVth International Symposium on Medicinal Chemistry, F. Awouters (editor) Elsevier Science B.V., 433-441, 1997 and WO97/16184 applied for by Warner-Lambert Co.; (viii) EP 0 635 501 A1 (European Application No. 94305305.8); and (ix) Tanaka, A. et al., *Inhibition of acyl-CoA:cholesterol O-acyltransferase. 2. Identification and structure-activity relationship of a novel series of N-alkyl-N-(heteroaryl-substituted benzyl)-N'-arylureas*, J. Med. Chem., *41*:2390-2410, 1998, all of which are herein incorporated by reference.

Particular ACAT inhibitor compounds useful with this invention include Compounds (i)-(ix) shown below and the pharmaceutically acceptable salts and esters thereof:



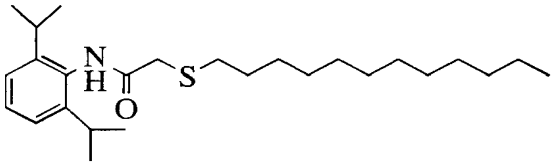
(i)

which is described in U.S. Patent No. 5,120,738;



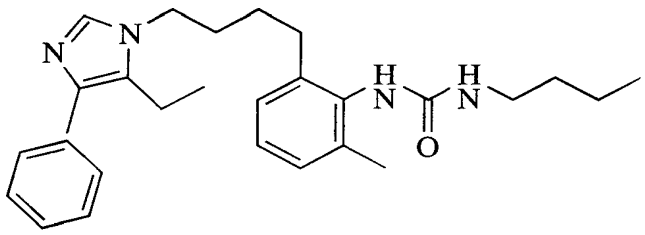
(ii)

which is described in U.S. Patent No. 5,340,807;



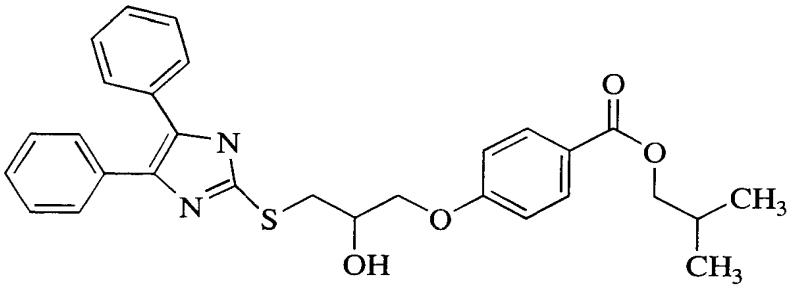
(iii)

which is described in U.S. Patent No. 5,475,130;



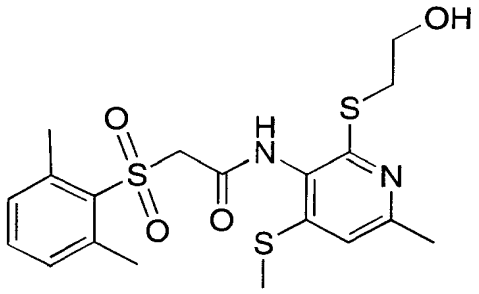
(iv)

which is described in U.S. Patent No. 5,668,136;



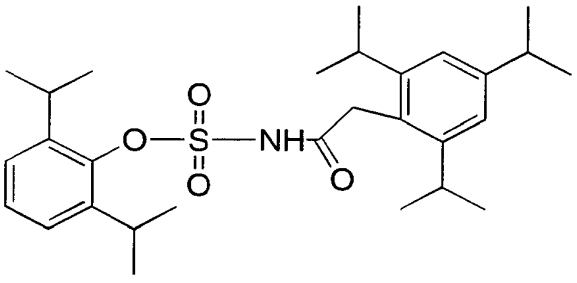
(v)

which is described in U.S. Patent No. 5,760, 087;



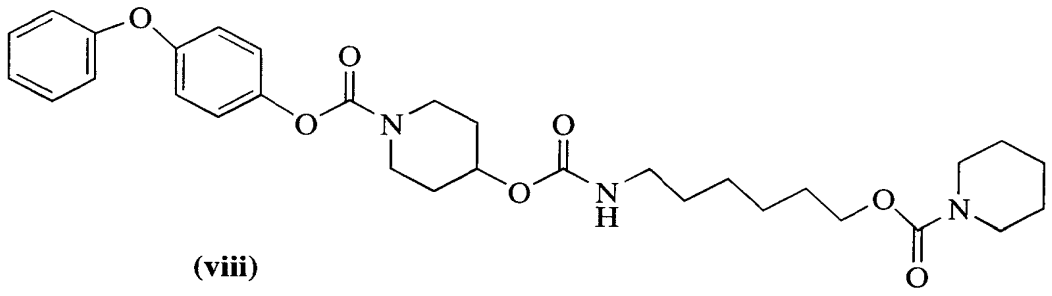
(vi)

which is described in WO96/26925;



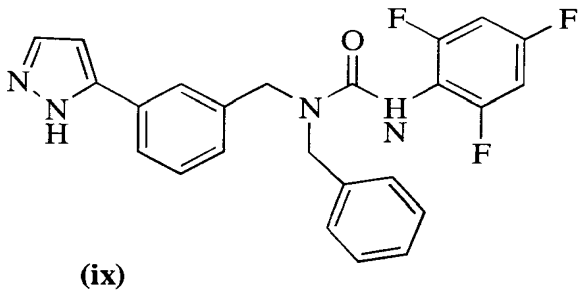
(vii)

which is described in the D. R. Sliskovic publication noted above,



(viii)

described in EP 0 635 501 A1 and



(ix)

described in the A. Tanaka et al., publication noted above.

The compounds of use in this invention may have one or more chiral centers and the present compounds may occur as racemates, racemic mixtures and as individual diasteriomers or enantiomers with all such isomeric forms and mixtures thereof being included within the scope of this invention. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates and hydrates, as well as anhydrous compositions, are encompassed within the scope of this invention. Some of the compounds described herein may contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The instant pharmaceutical combination comprising an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor includes administration of a single pharmaceutical dosage formulation which contains both the HMG-CoA reductase inhibitor and the ACAT inhibitor, as well as administration of each active agent in its own separate pharmaceutical dosage formulation. Where separate dosage

formulations are used, the HMG-CoA reductase inhibitor and the ACAT inhibitor can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially. The instant pharmaceutical combination is understood to include all these regimens. Administration in these various ways are suitable for the present invention as long as the beneficial pharmaceutical effect of the HMG-CoA reductase inhibitor and the ACAT inhibitor are realized by the patient at substantially the same time. Such beneficial effect is preferably achieved when the target blood level concentrations of each active drug are maintained at substantially the same time. It is preferred that the HMG-CoA reductase inhibitor and the ACAT inhibitor be co-administered concurrently on a once-a-day dosing schedule; however, varying dosing schedules, such as the HMG-CoA reductase inhibitor once per day and the ACAT inhibitor once, twice or more times per day, is also encompassed herein. A single oral dosage formulation comprised of both an HMG-CoA reductase inhibitor and the ACAT inhibitor is preferred. A single dosage formulation will provide convenience for the patient, which is an important consideration especially for patients who already have coronary heart disease and may be in need of multiple medications.

The term "patient" is intended herein to mean human patients who take an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor for any of the uses described herein. Administering of the drug combination to the patient includes both self-administration and administration to the patient by another person.

The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician. The dosage regimen utilizing an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt or ester thereof employed. Since two different active agents are being used together in a combination therapy, the potency of each of the agents and the interactive effects achieved by

combining them together must also be taken into account. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amounts needed to prevent, counter, or arrest the progress of the condition.

The ACAT inhibitor is intended to be administered daily in a synergistic therapeutically effective or prophylactically effective amount when used in combination with the HMG-CoA reductase inhibitor, and it has been found that such synergy is lost at a certain point as the dosage amount of the ACAT inhibitor increases. In particular, what is unexpected is that increased reductions in plasma cholesterol and triglyceride levels in mammals are not achieved by simply continuing to increase the dosage amounts of the ACAT inhibitor when given in combination with the HMG-CoA reductase inhibitor; rather, after reaching a synergistic plateau in efficacy, as the dosage amount of the ACAT inhibitor continues to increase for a given amount of HMG-CoA reductase inhibitor, the beneficial synergistic effects diminish and disappear, and eventually the reductions in cholesterol and triglycerides achieved with the drug combination can be less than the reductions that are achieved with the HMG-CoA reductase inhibitor alone.

A "synergistic therapeutically effective amount" and a "synergistic prophylactically effective amount " are both intended herein to mean a daily amount of an ACAT inhibitor which, when administered in combination with a given daily plasma cholesterol lowering amount, and particularly a plasma LDL cholesterol lowering amount, of an HMG-CoA reductase inhibitor, would achieve cholesterol (particularly LDL cholesterol) lowering and/or triglyceride lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone. For example, in humans, each doubling of the daily dosage amount of a statin, for example simvastatin, generally results in an additional 6% reduction in plasma LDL cholesterol level. Therefor, if a dosage amount of 5 mg per kg (mpk) of simvastatin reduced the plasma LDL cholesterol level by 10%, a doubled dosage of 10 mpk would reduce the plasma LDL cholesterol level by an additional 6% resulting in about a 16% reduction of the LDL cholesterol level. A further doubling of the simvastatin dose to 20 mpk (a four-fold dose increase over the initial 5 mpk dose) would reduce the plasma LDL cholesterol level by an additional 6% resulting in about a 22% reduction of the LDL cholesterol level. In this example, the synergistic therapeutically (or prophylactically) effective amount of ACAT inhibitor

contemplated by the instant invention would be the amount capable of lowering plasma LDL cholesterol by 22% or more when given in combination with 5 mpk simvastatin. More specifically, it can be seen based on the above discussion that with respect to LDL cholesterol, a "synergistic therapeutically effective amount" and a "synergistic prophylactically effective amount" are both intended herein to mean a daily amount of an ACAT inhibitor which, when administered in combination with a given daily plasma LDL cholesterol lowering amount of an HMG-CoA reductase inhibitor, can achieve LDL cholesterol lowering by the combination that is at least 12% greater than would be achieved by administration of the HMG-CoA reductase inhibitor alone. The 12% or more additional LDL lowering benefit provided by the ACAT inhibitor when used in combination with the HMG-CoA reductase inhibitor is essentially equivalent to the LDL lowering results obtainable with a four-fold increase in the dosage amount of the HMG-CoA reductase inhibitor administered alone.

In another embodiment of this invention, the daily dosage amount of ACAT inhibitor to be used with the instant combination therapy comprises that amount of ACAT inhibitor which, when administered in combination with a given amount of an HMG-CoA reductase inhibitor, (1) would achieve LDL cholesterol lowering and/or triglyceride lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone, and/or (2) is capable of lowering the amount of hepatic HMG-CoA synthase m-RNA that would be produced by the administration of the HMG-CoA reductase inhibitor alone by at least 20%. More particularly, the amount of ACAT inhibitor administered in combination with the HMG-CoA reductase inhibitor is capable of lowering the amount of hepatic HMG-CoA synthase m-RNA that would be produced by the administration of the HMG-CoA reductase inhibitor alone by about 20% to about 80%, for example reducing it by at least about 20%, 30%, 40%, 50%, 60%, 70% or 80%.

In a another embodiment, the daily dosage amount of ACAT inhibitor to be used with the instant combination therapy comprises that amount of ACAT inhibitor which, when administered in combination with a given amount of an HMG-CoA reductase inhibitor, (1) would achieve LDL cholesterol lowering and/or triglyceride lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone, and/or (2) is capable of lowering the amount of hepatic HMG-CoA reductase m-RNA that would be produced by the administration of the

HMG-CoA reductase inhibitor alone by at least 20%. More particularly, the amount of ACAT inhibitor administered in combination with the HMG-CoA reductase inhibitor is capable of lowering the amount of hepatic HMG-CoA reductase m-RNA that would be produced by the administration of the HMG-CoA reductase inhibitor alone by about 20% to about 80%, for example reducing it by at least about 20%, 30%, 40%, 50%, 60%, 70% or 80%.

In still another embodiment, the daily dosage amount of ACAT inhibitor to be used with the instant combination therapy comprises that amount of ACAT inhibitor which, when administered in combination with a given amount of an HMG-CoA reductase inhibitor, (1) would achieve LDL cholesterol lowering and/or triglyceride lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone, and/or (2) is capable of lowering cholesterol synthesis beyond the lowering attainable by the administration of the HMG-CoA reductase inhibitor alone by at least 20%. More particularly, the amount of ACAT inhibitor administered in combination with the HMG-CoA reductase inhibitor is capable of lowering cholesterol synthesis beyond the lowering attainable by administration of the HMG-CoA reductase inhibitor alone by at least 20% to about 80%, for example reducing it by at least about 20%, 30%, 40%, 50%, 60%, 70% or 80%.

Cholesterol synthesis may be estimated in man through the sterol balance method (see Grundy S.M. and Ahrens E.H., J. Lipid Res., *10*: p91, 1969, *Measurements of cholesterol turnover, synthesis, and absorption in man, carried out by isotope kinetic and sterol balance methods,* herein incorporated by reference) or through measurements of plasma or urinary mevalonate (see Parker T.S., McNamara, D.J., Brown, C.D., Kolb, R., Ahrens, E.H., Alberts, A.W., Tobert, J., Chen, J. and De Schepper, P.J., J. Clin. Invest. *74*: 795-804, 1984, *Plasma mevalonate as a measure of cholesterol synthesis in man*, herein incorporated by reference).

Even more particularly, for the methods described herein, the ACAT inhibitor can be administered to a patient in a dosage amount of 50 mg or less per day, for example from about 0.1 to 50 mg per day, particularly from 0.1 to 40 mg per day, more particularly from 0.1 to 30 mg per day, and most particularly from 0.1 to 20 mg per day. Examples of daily dosage amounts include but are not limited to 0.1, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 mg per day.

The daily synergistic therapeutically effective dosage amounts of the HMG-CoA reductase inhibitor are intended to be the same or similar to those amounts

which are employed for anti-hypercholesterolemic treatment and which are described in the Physicians' Desk Reference (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. For example. the oral dosage amount of HMG-CoA reductase inhibitor can be from about 0.1 to 200 mg/day, or from about 1 to 200 mg/day, preferably from about 0.1 to 100 mg/day, and more preferably from about 5 to 80 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages. The HMG-CoA reductase inhibitor may be administered from 1 to 4 times per day, and preferably once per day.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg and 80 mg; for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; for pravastatin sodium, 10 mg, 20 mg, and 40 mg; and for atorvastatin calcium, 10 mg, 20 mg, and 40 mg.

The instant combination therapy can be administered chronically in order to control the patient's cholesterol and triglyceride levels, and in order to gain the long-term benefits of atherosclerotic disease treatment and prevention; the drug combination can also be administered acutely when warranted.

Additional active agents may be used in combination with the HMG-CoA reductase inhibitor and ACAT inhibitor in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration. One or more additional active agents may be administered with instant combination therapy. The additional active agent or agents can be lipid lowering compounds or agents having other pharmaceutical activities, or agents that have both lipid-lowering effects and other pharmaceutical activities. Examples of additional active agents which may be employed include but are not limited to HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors); microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; human peroxisome proliferator activated receptor gamma (PPARγ) agonists including the compounds commonly referred to as glitazones for example troglitazone, pioglitazone and rosiglitazone and, including those compounds included within the structural class known as thiazolidinediones as well as those PPARγ agonists outside the

thiazolidinedione structural class; PPARα agonists such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil; PPAR dual α/γ agonists; cholesterol absorption inhibitors such as SCH-58235 also known as ezetimibe and 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone, which is described in U.S. Patent No.'s 5,767,115 and 5,846,966; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as vitamin C and E and beta carotene, beta-blockers; angiotensin II antagonists such as losartan; angiotensin converting enzyme inhibitors such as enalapril and captopril; calcium channel blockers such as nifedipine and diltiazam; endothelian antagonists; agents that enhance ABC1 gene expression; FXR and LXR ligands including both inhibitors and agonists; bisphosphonate compounds such as alendronate sodium; and cyclooxygenase-2 inhibitors.

The active agents employed in the instant combination therapy can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The instant invention includes the use of both oral rapid-release and time-controlled release pharmaceutical formulations. A particular example of an oral time-controlled release pharmaceutical formulation is described in U.S Patent No. 5,366,738. Oral formulations are preferred. Such pharmaceutical compositions are known to those of ordinary skill in the pharmaceutical arts; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

In the methods of the present invention, the active agents are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically

acceptable, inert carrier such as lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium stearate, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) can also be added to stabilize the dosage forms. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, carboxymethylcellulose, polyethylene glycol, waxes and the like.

The active drugs can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

Although the active agents of the present method may be administered in divided doses, for example two or three times daily, a single daily dose of each of the HMG-CoA reductase inhibitor and the ACAT inhibitor is preferred, with a single daily dose of both agents in a single pharmaceutical composition being most preferred.

The instant invention also encompasses a process for preparing a pharmaceutical composition comprising combining the HMG-CoA reductase inhibitor

and the ACAT inhibitor with a pharmaceutically acceptable carrier, as well as the pharmaceutical composition which is made by combining the HMG-CoA reductase inhibitor and the ACAT inhibitor with a pharmaceutically acceptable carrier.

Synergistic therapeutically effective amounts of an HMG-CoA reductase inhibitor and an ACAT inhibitor can be used together for the preparation of a medicament useful for reducing cholesterol synthesis, lowering plasma cholesterol levels, particulalry plasma LDL cholesterol levels, lowering plasma triglyceride levels, preventing or reducing the risk of developing atherosclerotic disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event. For example, the medicament may be comprised of an ACAT inhibitor in combination with about 0.1 mg to 100 mg of an HMG-CoA reductase inhibitor, or more particularly about 5 mg to 160 mg of the HMG-CoA reductase inhibitor. More specific amounts of HMG-CoA reductase inhibitor which may be used in the medicament preparation include 0.1 mg, 1 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg, as well as sub-milligram amounts of HMG-CoA reductase inhibitor's which have sufficient potency at such levels. As a particular example, the medicament may be comprised of an HMG-CoA reductase inhibitor in combination with about 0.1 to 50 mg of an ACAT inhibitor.

The instant invention also encompasses the use of a synergistic therapeutically effective amount of an HMG-CoA reductase inhibitor for the preparation of a medicament for combined use with a synergistic therapeutically effective amount of an ACAT inhibitor for reducing cholesterol synthesis, lowering plasma LDL cholesterol levels, lowering plasma triglyceride levels, preventing or reducing the risk of developing atherosclerotic disease, for halting or slowing the progression of atherosclerotic disease, or for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event. It also encompasses the use of a synergistic therapeutically effective amount of an ACAT inhibitor for the preparation of a medicament for the combined use with a synergistic therapeutically effective amount of an HMG-CoA reductase inhibitor for reducing cholesterol synthesis, lowering plasma cholesterol levels, particularly plasma LDL cholesterol levels, lowering plasma triglyceride levels, preventing or reducing the risk of developing atherosclerotic disease, for halting or slowing the progression of atherosclerotic disease, or for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event. The medicament or pharmaceutical combination

comprised of the HMG-Co reductase inhibitor and the ACAT inhibitor may also be prepared with one or more additional active agents, such as those described supra.

EXAMPLE

The effects of the ACAT inhibitors, compound (i) and compound (vi), and simvastatin on the plasma cholesterol levels in hamsters fed a cholesterol-free chow diet were studied. Compounds were mixed in milled chow diet and given to hamsters (10 hamsters per each treatment group). After 10 days treatment, hamsters were euthanized and their serum cholesterol levels were determined. The results of this study are presented in Figure 1. The data show that simvastatin at 0.025%, compound (vi) at 0.1% and compound (i) at 0.1% mixed in diet did not significantly affect plasma cholesterol levels. The combination of simvastatin at 0.025% with either compound (i) or compound (vi) at 0.1% showed significant cholesterol lowering in hamsters. This data shows a synergistic cholesterol lowering effect of these ACAT inhibitors when used in combination with simvastatin.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, specific effective dosage amounts other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the instant invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method for lowering plasma triglyceride levels comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in therapeutically effective amounts to a patient in need of such treatment.

2. A method for reducing cholesterol synthesis comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient in need of such treatment.

3. The method of claim 2 wherein the ACAT inhibitor is administered in an amount that can achieve lowering of cholesterol synthesis by the combination that is at least 20% greater than would be achieved by administration of the HMG-CoA reductase inhibitor alone.

4. A method of reducing plasma LDL cholesterol levels comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve LDL cholesterol lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone.

5. A method of reducing plasma LDL cholesterol levels comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve LDL cholesterol lowering by the combination that is at least 12% greater than would be achieved by administration of the HMG-CoA reductase inhibitor alone.

6. The method of claim 5 wherein the dosage amount of the ACAT inhibitor is less than 50 mg per day.

7. The method of claim 6 wherein the dosage amount of the ACAT inhibitor is from 0.1 to 40 mg per day.

8. The method of claim 7 wherein the dosage amount of the ACAT inhibitor is from 0.1 to 30 mg per day.

9. The method of claim 8 wherein the dosage amount of the ACAT inhibitor is from 0.1 to 20 mg per day.

10. A method of treating hypercholesterolemia comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient in need of such treatment, wherein the amount of ACAT inhibitor administered is capable of lowering the amount of hepatic HMG-CoA synthase m-RNA that would be produced by the administration of the HMG-CoA synthase inhibitor alone by at least 20%.

11. A method of treating hypercholesterolemia comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient in need of such treatment, wherein the amount of ACAT inhibitor administered is capable of lowering the amount of hepatic HMG-CoA reductase m-RNA that would be produced by the administration of the HMG-CoA reductase inhibitor alone by at least 20%.

12. A method of preventing the onset of or reducing the risk of developing atherosclerotic disease comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic prophylactically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve plasma LDL cholesterol lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone.

13. A method of treating atherosclerotic disease comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve plasma LDL cholesterol lowering by the combination that is equivalent to or greater than the

lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone.

14. A method of preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic prophylactically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve plasma LDL cholesterol lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone.

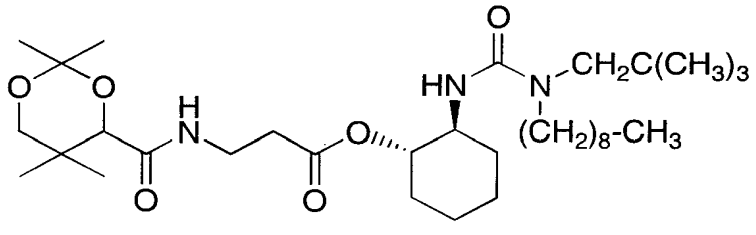
15. The method of Claim 4 wherein the HMG-CoA reductase inhibitor is selected from the lactone and dihydroxy open-acid forms of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, NK-104 and ZD-4522 and the pharmaceutically acceptable salts and esters thereof.

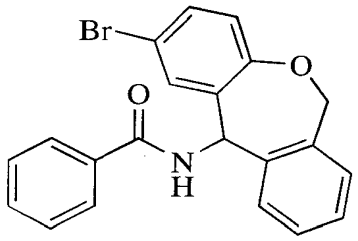
16. The method of Claim 15 wherein the HMG-CoA reductase inhibitor is selected from the lactone and dihydroxy open-acid forms of simvastatin and the pharmaceutically acceptable salts and esters thereof.

17. The method of Claim 15 wherein the HMG-CoA reductase inhibitor is selected from the lactone and dihydroxy open-acid forms of lovastatin and the pharmaceutically acceptable salts and esters thereof.

18. The method of claim 4 wherein the ACAT inhibitor is selected from the group consisting of:

(i)





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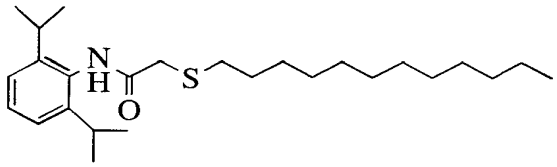
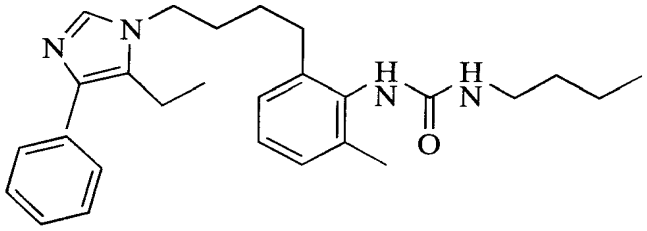
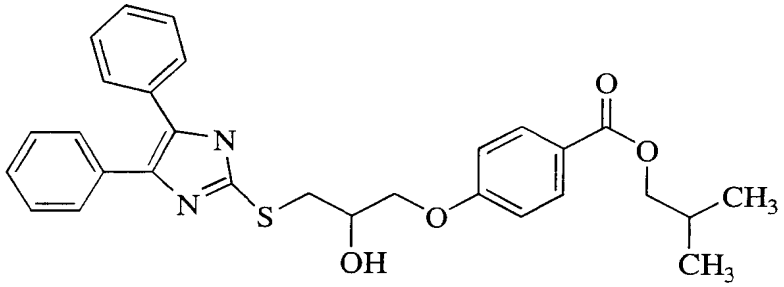


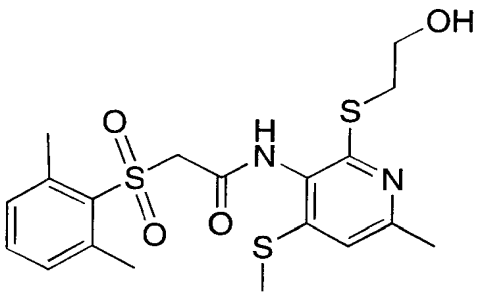
(iii)



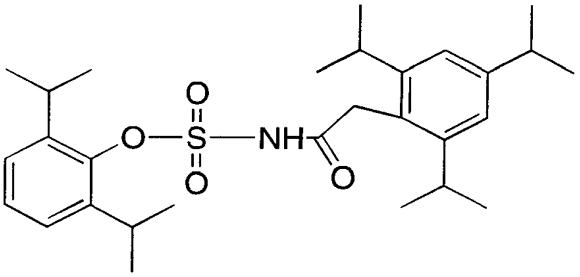
(iv)



(v)



(vi)



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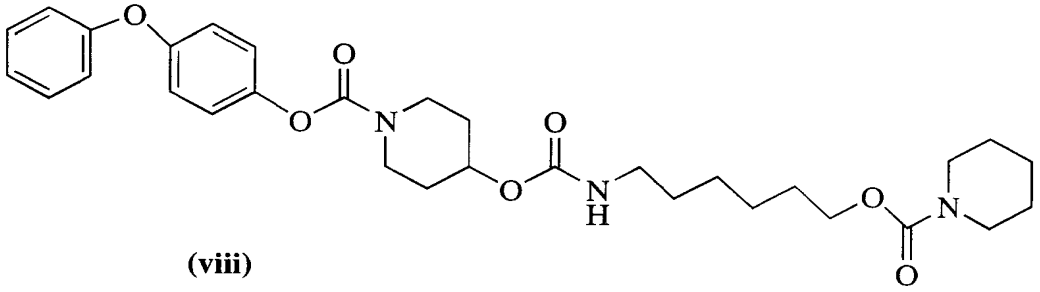
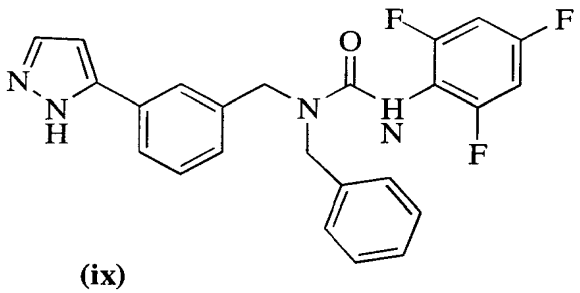


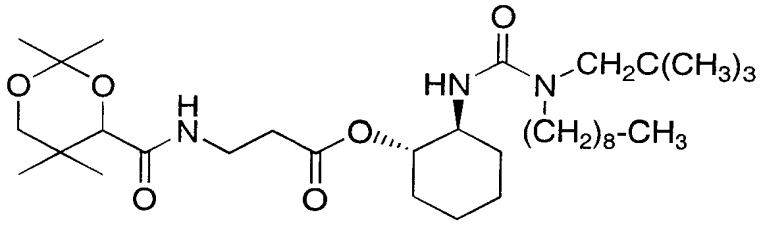
(viii)



(ix)

and the pharmaceutically acceptable salts and esters thereof.

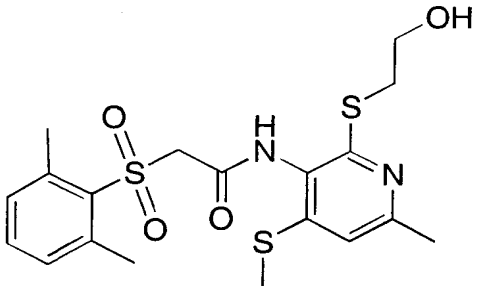
19. The method of claim 18 wherein the ACAT inhibitor is



(i)

and the pharmaceutically acceptable salts thereof.

20. The method of claim 18 wherein the ACAT inhibitor is



(vi)

and the pharmaceutically acceptable salts and esters thereof.

21. A pharmaceutical composition comprising an HMG-CoA reductase inhibitor and an ACAT inhibitor in synergistic therapeutically effective amounts, and a pharmaceutically acceptable carrier.

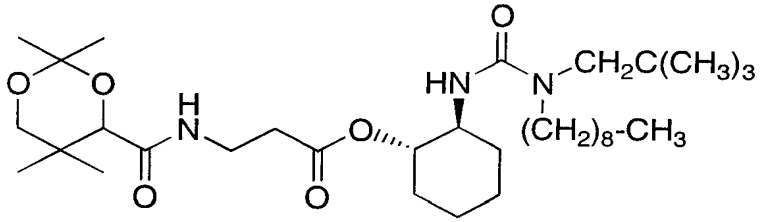
22. The composition of Claim 21 wherein the HMG-CoA reductase inhibitor is selected from the lactone and dihydroxy open-acid forms of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, NK-104 and ZD-4522 and the pharmaceutically acceptable salts and esters thereof.

23. The composition of Claim 22 wherein the HMG-CoA reductase inhibitor is selected from the lactone and dihydroxy open-acid forms of simvastatin and the pharmaceutically acceptable salts and esters thereof.

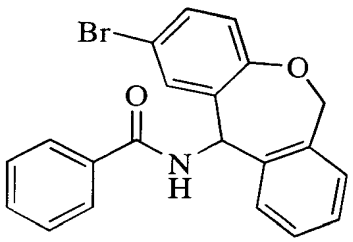
24. The composition of Claim 22 wherein the HMG-CoA reductase inhibitor is selected from the lactone and dihydroxy open-acid forms of lovastatin and the pharmaceutically salts and esters thereof.

25. The composition of Claim 21 wherein the ACAT inhibitor is selected from the group consisting of:

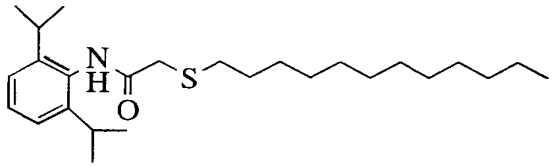
(i)

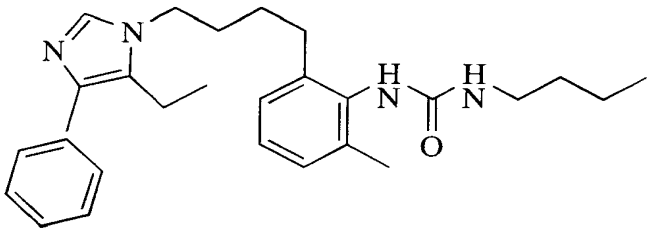


(ii)



(iii)





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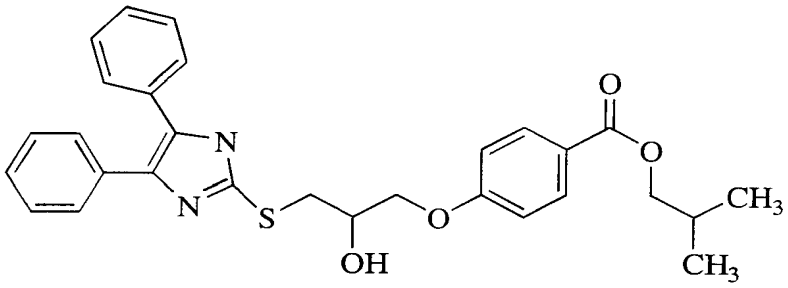

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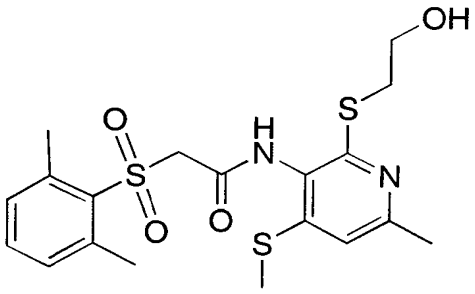
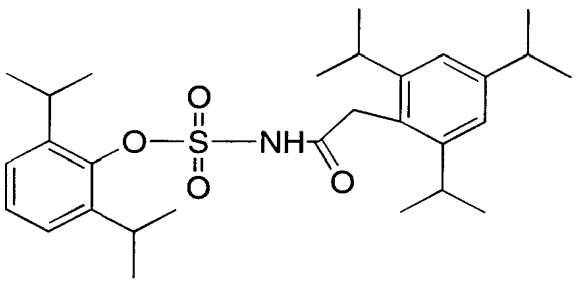
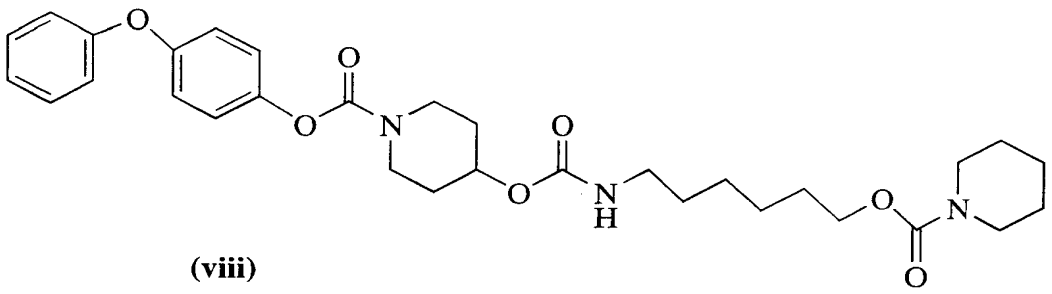


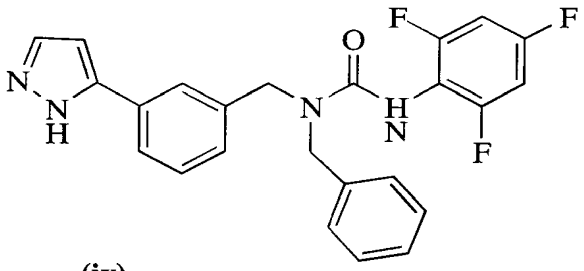
(vi)



(vii)



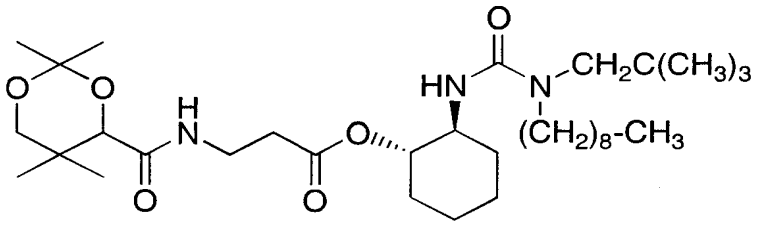
(viii)



(ix)

and the pharmaceutically acceptable salts and esters thereof.

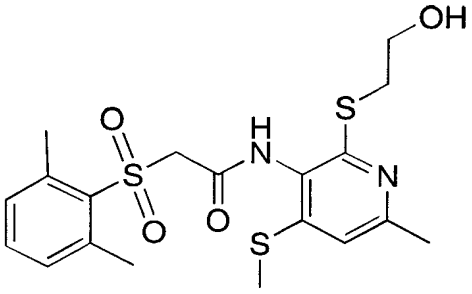
26. The composition of Claim 25 wherein the ACAT inhibitor is



(i)

and the pharmaceutically acceptable salts thereof.

27. The composition of Claim 25 wherein the ACAT inhibitor is



and the pharmaceutically acceptable salts and esters thereof.

28. A process for preparing the pharmaceutical composition of claim 21 comprising combining the HMG-CoA reductase inhibitor with the ACAT inhibitor and the pharmaceutically acceptable carrier.

29. A pharmaceutical composition made by combining an HMG-CoA reductase inhibitor and an ACAT inhibitor in synergistic therapeutically effective amounts, and a pharmaceutically acceptable carrier.

30. A method of reducing plasma cholesterol levels comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve cholesterol lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone.

31. The method of claim 30 wherein the dosage amount of the ACAT inhibitor is less than 50 mg per day.

32. The method of claim 31 wherein the dosage amount of the ACAT inhibitor is from 0.1 to 40 mg per day.

33. The method of claim 32 wherein the dosage amount of the ACAT inhibitor is from 0.1 to 30 mg per day.

34. The method of claim 33 wherein the dosage amount of the ACAT inhibitor is from 0.1 to 20 mg per day.

35. A method of preventing the onset of or reducing the risk of developing atherosclerotic disease comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic prophylactically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve plasma cholesterol lowering by the combination that is

equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone.

36. A method of treating atherosclerotic disease comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic therapeutically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve plasma cholesterol lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone.

37. A method of preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising administering an HMG-CoA reductase inhibitor in combination with an ACAT inhibitor in synergistic prophylactically effective amounts to a patient in need of such treatment, wherein the ACAT inhibitor is administered in an amount that can achieve plasma cholesterol lowering by the combination that is equivalent to or greater than the lowering that would be achieved by administering a four-fold greater dosage amount of the HMG-CoA reductase inhibitor alone.

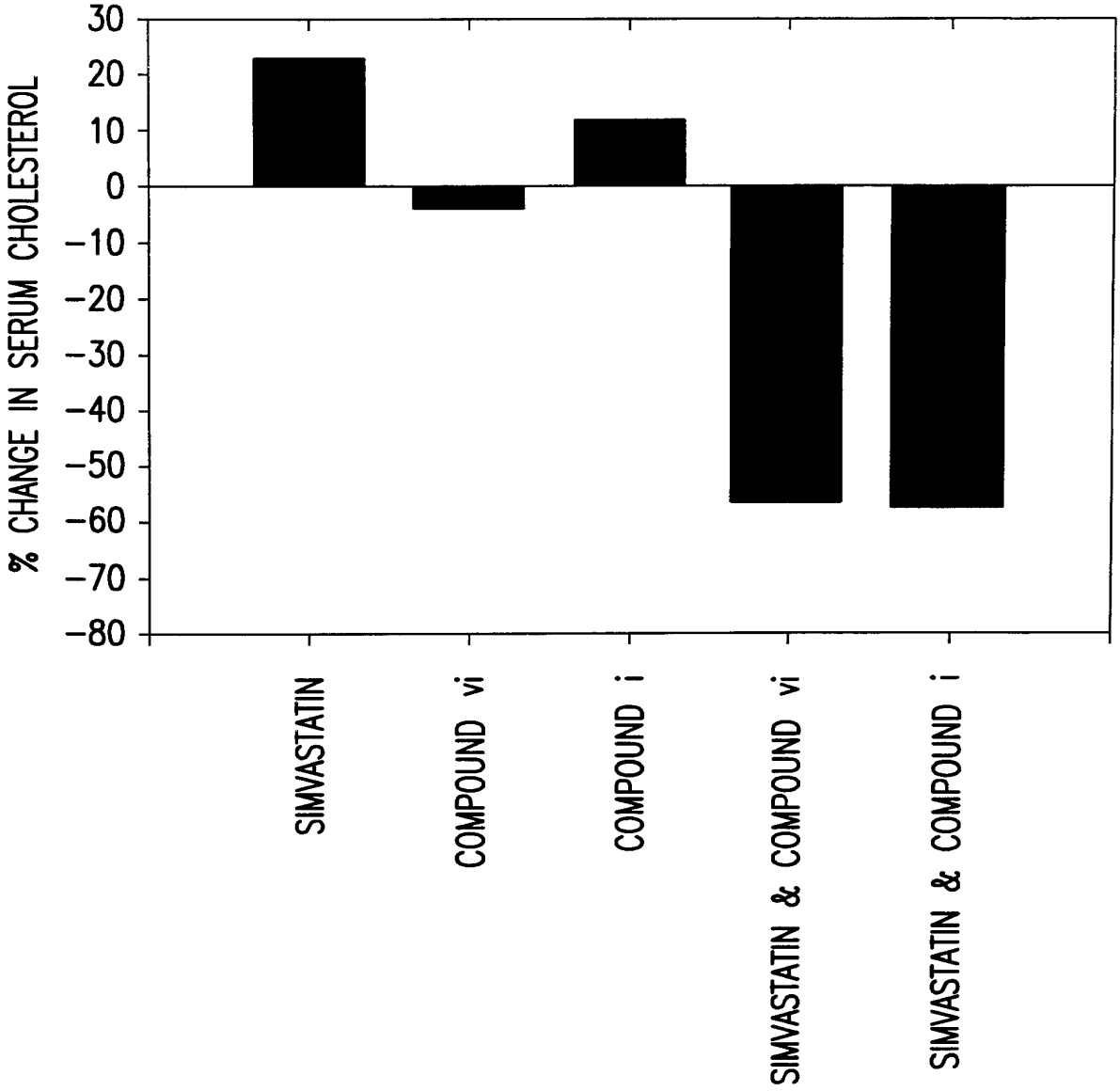

% CHANGE IN SERUM CHOLESTEROL
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
SIMVASTATIN
COMPOUND vi
COMPOUND i
SIMVASTATIN & COMPOUND vi
SIMVASTATIN & COMPOUND i

FIG.1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/26414

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/435, 31/405, 31/40, 31/35, 31/18, 31/16

US CL :514/ 277, 415, 423, 460, 547, 602, 603, 604, 625

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/ 277, 415, 423, 460, 547, 602, 603, 604, 625

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 97/16184 A1 (WARNER-LAMBERT COMPANY) 09 May 1997 (09.05.97), see page 2, lines 7-23, page 3, line 26 - page 5, line 4, page 5, line 34 - page 8, line 31.	1-6, 10-25, 27-30 and 35-37 --- 1-37

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
28 NOVEMBER 2000

Date of mailing of the international search report
31 JAN 2001

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